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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/659,408
Filing Date: September 10, 2003
Appellant(s): PARIKH ET AL.

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Attorney M. Henry Heines
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 11, 2006 appealing from the Office action mailed April 12, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 2002/0193698	Moilanen et al.	12-2002
US 2003/0073919	Hampton et al.	4-2003

Kharitonov et al. Monaldi Arch. Chest Dis., "Nitric Oxide in Exhaled Air is a New Marker of Airway Inflammation," 1996, 51(6), pp 533-537.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(a) **Claims 18-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moilanen et al. (US 2002/0193698) in view of Kharitonov et al. (*Monaldi Arch. Chest Dis.*, "Nitric Oxide in Exhaled Air is a New Marker of Airway Inflammation," 1996, *51(6)*, pp 533-537; IDS).**

Moilanen teaches **a method for measuring nitric oxide concentration in exhaled air** through a blow tube of measuring equipment. The method is used to diagnose an inflammatory lung disease in a patient whereby **an increased nitric oxide concentration indicates an inflammatory lung disease,** such as alveolitis (abstract).

Moilanen teaches that exhaled nitric oxide (eNO) concentration is higher than normal in subjects suffering from inflammatory lung diseases (e.g. asthma and alveolitis). The increased concentration of eNO is attributed to inflammation in the lungs, and can therefor be used as an indicator of inflammatory disease [0002]. The [eNO] can be measured by an analyzer intended for that purpose. In known measuring methods, a person exhales into an analyzer such that the flow rate of the exhaled air remains substantially constant. By this measuring method it is possible to detect a rise in the nitric oxide concentration of the exhaled air and thus to conclude, on the basis of the increased nitric oxide concentration, that there is inflammation in the lungs [0003].

Moilanen teaches in Figures 2 and 3 graphs of exhaled NO concentration ([eNO]) in units of ppb versus exhalation rate in units of ml/s for healthy patients (Figs. 2-3) and patients with asthma (Figs. 2-3) and alveolitis (Fig. 2). It is clear from the graph of Fig. 2 that a healthy patient with **an exhalation rate of approximately 50 ml/s** has **an [eNO] of about 20 ppb**, whereas those suffering from inflammatory diseases have higher [eNO]s. The bronchial NO flux of patients with asthma is higher than that of the healthy persons or the patients with alveolitis because of bronchial inflammation. The patients with alveolitis suffering from alveolar inflammation have, in turn, higher alveolar NO concentration than healthy persons or asthmatics [0026]. Figure 3 is specific to the [eNO] of children who are considered "healthy" and those diagnosed with asthma [0027]. A healthy child has an [eNO] of approximately **10 ppb** at an **exhalation rate of approximately 50 ml/s**, whereas an asthmatic child has an eNO of approximately 50 ppb at the same exhalation rate. Because very low exhalation flow rates have been used in the measurements of Fig. 2, it is possible to calculate the nitric oxide concentration

of the bronchial wall tissue and the NO diffusion capacity in said tissue. On the basis of these calculated variables, **it is possible to draw conclusions on the intensity and location of the inflammation in the lungs** in the same manner as in the material of FIG. 2 [0027].

Moilanen teaches the results of studies conducted prior to the publication of US 2002/0193698 [0029]-[0030], wherein **patients with asthma** undergoing an 8 week treatment of inhaled glucocorticoids exhibited a significant decrease in bronchial NO flux **after one week of treatment** and "normal" NO flux **after 8 weeks of treatment** compared to healthy controls (i.e. a baseline). Moilanen states that the results of their previous studies "support the role of present invention in differential diagnosis of alveolar and bronchial inflammatory diseases. The results also suggest that **the present method can be used to follow-up drug treatment of inflammatory lung diseases and provide means to assess the efficacy of such treatment** [0031]."

Moilanen lacks the express teaching of modifying active dosages used in treatment, changing the active agent, and subsequently evaluating the effects of these treatment protocol changes.

Kharitonov teaches that it is known in the art that **exhaled nitric oxide** (NO) is increased in patients with inflammatory diseases of the airways, such as **asthma** and bronchiectasis and **may be modulated by inhaled corticosteroids** (p 533, right hand column, 2nd paragraph, 2nd sentence). Corticosteroids are known medicaments.

Kharitonov suggest that exhaled NO may provide a noninvasive means of monitoring inflammation in the respiratory tract (p 533, right hand column, 3rd paragraph, 1st sentence).

Kharitonov teaches that it is suggested in the art that in inflammatory diseases increases in exhaled NO are due to induction of a third isoform of the NO synthase enzyme (iNOS). It is known in the art that glucocorticoids inhibit the induction of iNOS in epithelial cells *in vitro* and *in vivo*, and **reduce exhaled NO levels in asthmatic patients to normal** (p 534, right hand column, 2nd paragraph, 1st and last sentences and left hand column, 1st paragraph, 1st line).

Kharitonov teaches that regarding asthma, there is now persuasive evidence **that levels of NO are increased in association with airway inflammation and are decreased with anti-inflammatory therapy** (p 535, 1st paragraph, 1st sentence in the section entitled "Clinical Relevance of Exhaled NO" with the sub-heading "Asthma").

Kharitonov teaches that a double-blind study of **inhaled budesonide**, a synthetic anti-inflammatory corticosteroid, **showed a progressive reduction of exhaled NO down to normal values after three weeks of therapy** (p 535, left hand column, 2nd paragraph, 4th sentence in the section entitled "Effects of Therapy").

Kharitonov summarizes the state of the prior art by stating that the advantage of exhaled NO is that the measurement is completely non-invasive and **can be performed repeatedly**. In addition, because the measurement is not specific, absolute values are less important than serial measurements in individual patients. For example, the value of this approach in asthmatic patients has been shown **where the dose of the inhaled steroid is changed**, resulting in **increased levels of NO when the dose is reduced and lower levels of NO when the dose is increased**. Reduction of eNO levels is observed in anti-inflammatory treatment and may be used in **monitoring whether therapy is adequate** and **to ascertain the therapeutic effectiveness of new antiasthma drugs** (e.g. selective phosphodiesterase inhibitors, leukotriene

antagonists and synthesis inhibitors, and immunomodulators). Because the measurement of eNO is precise and reproducible, it **may facilitate dose-response effects** with anti-inflammatory treatments (p 537, right hand column, "Summary" section).

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Moilanen and Kharitonov, because both references teach the utility of monitoring exhaled nitric oxide levels as a metric to evaluate anti-inflammatory treatment. A skilled artisan would have been motivated to combine the teachings of Moilanen and Kharitonov, because both references describe similar methods and Moilanen provides data comparing the exhaled nitric oxide profiles of healthy patients, asthmatics, and patients suffering from alveolitis, as a function of the flow rate of exhaled air. It would have been apparent to a skilled artisan that one would use the curve for exhaled nitric oxide (NO) of healthy patients provided by Moilanen as a baseline to ascertain the effectiveness of treatment because the achievement of normative exhaled nitric oxide levels is obviously a goal of these therapeutic methods. It would have been apparent that a skilled artisan would use a patient's initial eNO measurements as a baseline for comparison to ascertain whether treatment was effective.

Although the prior art references do not expressly discuss the use of "trends," it is obvious from Kharitonov's teaching of studies of budesonide treatment of asthmatics that the phrase "progressive reduction of exhaled NO" implies an observed trend, the use of said observation, and the artisan's practice of making multiple measurements over a period of time – three weeks in the study referred to by Kharitonov. A skilled artisan aware of the teachings of Kharitonov would understand that changing the dosage of active agent used would be expected

to affect the observed eNO levels and said artisan would be motivated to adjust the dosage amount appropriately to improve a patient's response to treatment. It would also have been apparent to a skilled artisan that changing the active agent used could result in increased or reduced NO levels, requiring monitoring to ascertain the effect of the new therapeutic drug, and subsequent appropriate adjustment of the therapy frequency and dosage, because Kharitonov stated that eNO measurement "may facilitate the measurement of dose-response effects with anti-inflammatory treatments." Therefore, due to the aforementioned reasoning, a skilled artisan would have had a reasonable expectation of success upon combination of the prior art references and claims 18-27 are *prima facie* obvious over the teachings of the prior art.

(b) **Claims 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hampton et al. (US 2003/0073919) in view of Moilanen et al. (US 2002/0193698).**

Hampton teaches **techniques for identifying and guiding treatment for medical conditions**, based upon the carbon dioxide concentration in the patient's breath. The techniques of the invention may further be used **to monitor the effectiveness of the treatment** (abstract). The method taught by Hampton is directed to techniques for rapidly and reliably distinguishing **obstructive lung disease** from restrictive lung disease. In addition, the invention is directed to techniques for monitoring the response of the patient to treatment for the condition [0010]. The term "obstructive lung disease" encompasses asthma, which is a disease associated with inflammation of the lungs.

Hampton's method may take into consideration, for example, the duration of a steady rise of the concentration of carbon dioxide in the breath or the rate of increase of the concentration of

carbon dioxide, as measured by the initial angle and slope of the capnogram. The method may also **compare the carbon dioxide concentration in the breath with a characteristic curve**. The method **may further include monitoring the condition of the patient following treatment** [0013]. The method may also be used to guide treatment, **including determining the presence of lung conditions, determining the severity of the conditions, and selecting medicaments to treat the conditions** [0015]. For example, system 70 helps to determine the nature of the condition and further helps guide treatment of the patient. Processor 82 may report the severity of the condition, **suggest a medicine for the condition**, **recommend that the measurements be repeated**, or that the patient be instructed to breathe in a particular manner. In some circumstances, such as **the treatment of some forms of asthma**, proper treatment produces a prompt improvement in the condition of the patient and **this improvement can be monitored.** The invention need not be embodied in a method that analyzes only carbon dioxide concentration in the breath, but may include other diagnostic measurements such as measurements of heart rate, respiration rate, blood pressure, electrocardiogram, and blood oxygenation [0052]-[0055].

Hampton lacks the teaching of the measurement of exhaled nitric oxide.

The teachings of Moilanen have been set forth above.

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Hampton and Moilanen, because both carbon dioxide and nitric oxide are gases present in exhaled air that have been measured as a means to monitor a medical condition (e.g. asthma) and the treatment of said condition. A skilled artisan

would have been further motivated to combine the teachings Hampton and Moilanen, because Moilanen provides data useful in establishing the "normative levels" of exhaled NO and Hampton's method facilitates the use of a processor (i.e. computer) to analyze clinical data and suggest means of changing (i.e. guiding) a patient's treatment. Because both prior art references teach methods of monitoring respiratory conditions by the measurement of the concentration of exhaled gases -either carbon dioxide or nitric oxide- and Moilanen's teaching provide data useful in establishing a baseline of "normal levels" of exhaled nitric oxide, a skilled artisan would have had a reasonable expectation of success upon combination. It would have been apparent to a skilled artisan that Hampton's teaching of comparing the concentration of carbon dioxide in breath to a characteristic curve could be modified to compare a patient's exhaled nitric oxide measurements to characteristic curves (i.e. baselines) to evaluate treatment efficacy. Using Hampton's teachings, in which the processor reports the condition's severity and recommends medications, a person of ordinary skill in the art at the time of the instant invention would have obviously been able to ascertain whether the appropriate step in treatment required a change in medication and or dosage frequency. Likewise, given the severity of the condition, the skilled artisan would be capable of determining the required frequency of [eNO] measurement to properly evaluate treatment progress.

(10) Response to Argument

Appellants' traversal of the rejections of record under 35 U.S.C. § 103(a) are based on the following general arguments:

(i) The prior art lacks the teaching of obtaining a baseline utilizing multiple measurements made at different frequencies.

(ii) The prior art lacks the teaching of making a comparison of repeated measurements with a baseline.

(iii) The prior art lacks the teaching of modifying a treatment protocol after comparison of measurements with a baseline.

The Examiner respectfully disagrees with Appellants' arguments.

(a) Addressing Appellants' traversal arguments with respect to the rejection of claims 18-27 under 35 U.S.C. 103(a) as being unpatentable over Moilanen et al. (US 2002/0193698) in view of Kharitonov et al. (*Monaldi Arch. Chest Dis.*), it is noted that it would have been apparent to a skilled artisan that one would use the curve for exhaled nitric oxide (NO) of healthy patients provided by Moilanen as a baseline to ascertain the effectiveness of treatment because the achievement of normative exhaled nitric oxide levels is obviously a goal of these therapeutic methods. Moilanen also teaches in Figures 2 and 3, curves for asthmatics and those suffering from alveolitis (see also [0026]). Curves, such as those taught by Moilanen (e.g. See Figures 2 and 3), are obviously graphical representations of trends. The curves in Moilanen's Fig. 2 were based on measurements made at four different exhalation flow rates for 40 patients with asthma, 17 patients with alveolitis, and 57 healthy reference persons [0026], whereas the curves depicted in Fig. 3 were based upon measurements of exhaled air of one asthmatic child and one healthy child made at 5 different exhalation flow rates (10, 50, 100, 200, and 300 mL/s). These curves clearly provide a baseline and demonstrate to the skilled artisan how one would establish a baseline. Furthermore, it is common knowledge in the medical art to perform an initial

evaluation of a patient's condition and overall health (i.e. establish a baseline) as well as subsequent evaluation to ascertain a patient's response to a given treatment protocol. Notwithstanding the teachings of Moilanen and what is commonly known in the art, it is obvious that in Kharitonov's teaching of studies of budesonide treatment of asthmatics that the phrase "progressive reduction of exhaled NO" implies an observed trend, the use of said observation, and the artisan's practice of making multiple measurements over a period of time – three weeks in the study referred to by Kharitonov. It is also emphasized that Kharitonov teaches (pg. 537, right hand column, "Summary" section) that the prior art recognizes the administration of corticosteroids can reduce eNO levels and the change of eNO levels may be used to monitor and evaluate the effectiveness of a given therapy as well as to determine the effectiveness of new antiasthma drugs. Therefore, the Examiner concludes that claims 18-27 are *prima facie* obvious over the combined teachings of Moilanen et al. (US 2002/0193698) in view of Kharitonov et al. (*Monaldi Arch. Chest Dis.*).

(b) Addressing Appellants' traversal arguments with respect to the rejection of claims 18-24 under 35 U.S.C. 103(a) as being unpatentable over Hampton et al. (US 2003/0073919) in view of Moilanen et al. (US 2002/0193698) it is noted that Hampton teaches a method to guide treatment, utilizing a processor, wherein the steps include (i) determining the presence of lung conditions, (ii) determining the severity of the conditions, (iii) selecting medicaments to treat the conditions, (iv) recommending the repetition of measurements or that the patient be instructed to breathe in a particular manner ([0015] and [0052]-[0055]). Hampton's method focuses on the analysis of carbon dioxide, but is taught as being useful in the other diagnostic measurements. The combined teachings of Hampton and Moilanen, however, do teach the measurement of

exhaled nitric oxide (eNO), the determination of a baseline via eNO measurements, and the modification of a treatment protocol by changing the medicaments used. As stated above in this Examiner's answer, Moilanen does provide the teachings of establishing baselines via multiple measurements of exhaled nitric oxide. Furthermore, it is noted that the prior art recognizes the use of eNO as a way to evaluate and monitor the treatment of asthma (see Kharitonov). Thus, the Examiner concludes that claims 18-24 are *prima facie* obvious over the combined teachings of Hampton et al. (US 2003/0073919) in view of Moilanen et al. (US 2002/0193698).

For the above reasons, it is believed that the rejections should be sustained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

Respectfully submitted,

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER

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